Randomized phase III PITCAP trial and meta-analysis of induction chemotherapy followed by thoracic irradiation with or without concurrent taxane-based chemotherapy in locally advanced NSCLC


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Abstract
Background

Chemotherapy and radiotherapy combination is standard of care in the treatment of inoperable stage III non-small cell lung cancer (NSCLC). We aimed at assessing whether the addition of concurrent taxane-based chemotherapy to thoracic irradiation following platinum-taxane-based induction chemotherapy was able to improve treatment outcome.

Patients and methods

Patients with inoperable stage III NSCLC were randomized in PITCAP trial to receive 2 cycles of induction chemotherapy with cisplatin or carboplatin and paclitaxel followed by 60-61.2 Gy continuous thoracic irradiation (control arm) or by same radiotherapy with concomitant weekly paclitaxel (experimental arm). Furthermore, we performed a systematic review and a literature-based meta-analysis including all studies in which, after induction chemotherapy, a concurrent taxane-based chemo-radiotherapy program was compared to thoracic radiotherapy alone in locally advanced NSCLC. Primary measure of outcome in the meta-analysis was probability of 1-year survival.

Results

In the PITCAP trial, at the time of the second planned interim analysis, when 151 patients were randomized, accrual was terminated, due to slow recruitment. With a median follow-up of 6.1 years, median survival was 13.2 vs. 15.1 months, with a 3-year survival rate of 19.5% vs. 21.2% in the control and experimental arm, respectively (HR: 0.97; 95%CI 0.69-1.36; p = 0.845). No significant difference was observed in overall response rate (54% vs 52%) and progression-free survival (median 6.7 vs 9.2 months, in the control and experimental arm, respectively). Treatment toxicity was manageable in both arms (grade 3-4 esophagitis was 4.3% vs 10% in the control and experimental arm, respectively; p = 0.278). The meta-analysis, including 5 trials (n = 866), confirmed the lack of a meaningful effect on 1-year overall survival (OR: 1.17; 95%CI 0.75-1.82) of single agent taxane added concurrently to thoracic radiotherapy.
Conclusions

The results of PITCAP trial along with those of the meta-analysis do not support a clinically meaningful benefit with the addition of single agent taxane given concurrently to thoracic irradiation after platinum-based chemotherapy induction in locally advanced inoperable NSCLC.
Introduction

Lung cancer still represents the leading cause of cancer death in developed countries [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of all lung cancer cases and is characterized by advanced inoperable stage at diagnosis in most patients and by a very low cure-rate. While the standard of care of metastatic disease is represented by systemic therapy alone, optimal management of locally advanced inoperable disease, representing 20-30% of all NSCLC cases, entails the combined use of chemotherapy and radiotherapy. Chemo-radiotherapy combination may lead to a 5-year overall survival rate of approximately 20-30% [2].

In the context of multidisciplinary treatment, according to the results of several randomized studies and meta-analyses, timing of radiotherapy is important, given that early administration of radiotherapy concurrently with chemotherapy appears to be associated with better outcome, albeit producing increased local and systemic toxicity [3]. On the contrary, when using concurrent chemoradiation, evidence has shown no benefit by adding induction or consolidation chemotherapy [4, 5].

In the context of combined chemo-radiation treatment of NSCLC, platinum-based regimens, such as carboplatin-paclitaxel, cisplatin-etoposide or cisplatin-vinorelbine are recommended [6]. Concerning dose and schedule of radiotherapy, doses of 60-65 Gy delivered high-energy linear accelerators in 30-32 daily fractions are regarded as the standard of care [6]; increased dose of radiation and varied fractionation such as hyper or hypo-fractionation has not led to significantly improved results in overall survival [2,7,8].

Despite the evidence that concurrent chemo-radiation is superior in terms of survival outcome compared to sequential treatment [3], its use in real world clinical practice is limited by several factors including increased toxicity, too large volume disease to irradiate, advanced age, poor performance status (PS), presence of comorbidities and, in some cases, radiotherapy waiting lists. For these reasons, according to recent surveys, particularly in Europe [9, 10], but also in US [11], in clinical practice sequential chemo-radiotherapy protocols are still used in a large proportion of patients with locally advanced inoperable NSCLC. In this context, little evidence has been produced
about the potential benefit of adding chemotherapy concurrently to thoracic irradiation delivered after induction chemotherapy [12].

Given this background, our PITCAP (Progetto Interdisciplinare Terapia Carcinoma Polmonare) study was designed to verify whether the addition of a low-toxicity profile chemotherapy regimen such as weekly paclitaxel, given concurrently with thoracic irradiation after platinum-based induction chemotherapy was able to improve clinical outcome as compared to standard sequential chemo-radiotherapy in locally advanced inoperable NSCLC. Since we were aware of other few studies [13-17] with similar design and objective, we also performed a systematic review and a literature-based meta-analysis (TROCODILE meta-analysis, Taxane-based chemo-RadiOtherapy COmpared with raDIotherapy aLonE after induction chemotherapy in locally advanced Non-Small-Cell Lung Cancer) including all randomized trials addressing the same scientific question.
Patients and methods

Study design

Eligible patients were required to have: cytologically or histologically-confirmed newly-diagnosed NSCLC; inoperable clinical stage III disease with absence of pleural or pericardial effusion, supraclavicular node metastasis or esophageal or cardiac or spinal cord infiltration; age ≤ 70 years; ECOG performance status (PS) ≤ 1; and FEV1 (Forced Expiratory Volume one second) ≥ 1L; normal hepatic, renal and cardiac functions; absence of weight loss ≥ 10% in the previous 6 months; no prior chemotherapy and/or radiotherapy. Treatment in the control arm consisted of 2 cycles of paclitaxel 200 mg/m² combined with either carboplatin AUC 6 or cisplatin 80 mg/m² (at investigator choice) day 1 every 3 weeks followed by continuous thoracic irradiation either 60 Gy/30 fractions (200 cGy/fraction 5 days/week for 6 weeks, 22 fractions plus 8 boost fractions) or 61.2 Gy/34 fractions (180 cGy/fraction 5 days/week for 7 weeks, 25 fractions plus 9 boost fractions) (at investigator choice) delivered by high energy (4 MeV or higher) linear accelerator within 21-35 days from the 2nd chemotherapy induction course to the GTV (gross tumor volume) plus 2 cm margin as assessed by baseline CT scan. Experimental arm consisted of identical induction chemotherapy and thoracic irradiation with the addition of paclitaxel 60 mg/m² weekly for 6-7 weeks concurrently to thoracic irradiation. Patients were assessed at baseline with total body CT scan, pulmonary function tests and complete blood count and chemistry.

The study was conducted under the auspices of the Italian cooperative group FONICAP (Forza Operativa Nazionale Carcinoma Polmonare) and approved by Ethical Committee/Institutional Review Boards of all participating Institutions.

Statistical considerations

PITCAP trial

The primary objective of this randomized phase III trial was to assess the efficacy of adding weekly paclitaxel to standard thoracic irradiation after platinum-paclitaxel induction chemotherapy. Primary
end-point was overall survival (calculated as the time between randomization and death from any cause, or date of last follow-up visit for alive patients), while secondary end-points included progression-free survival (calculated as the time from randomization to the date of progressive disease or death, or date of last follow-up visit for patients alive without progression), response rate (measured according to WHO criteria) and toxicity (measured according to WHO/ECOG/RTOG criteria).

Planned accrual was 300 patients, in order to detect at least 30% mortality reduction with the addition of concurrent chemotherapy in the experimental arm ($\alpha = 5\%$; $\beta = 20\%$). The enrollment, according to the study protocol, was stopped after the inclusion of 151 patients due to the low observed accrual rate. Patients were centrally assigned in a 1:1 ratio to receive concurrent chemo-radiotherapy (experimental group) or radiotherapy alone (control group) after induction treatment. Randomization was stratified by clinical site.

The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method. Distributions of time-to-event variables were estimated with the use of the Kaplan–Meier product-limit method. The log-rank test was used as the primary analysis for comparison of treatment groups. Cox proportional-hazards modeling was also performed as supportive analyses, with xxx as covariates. The objective response rate and the incidence of adverse events in the two groups were compared with the use of the chi-square test for heterogeneity or with Fisher’s exact test when appropriate. All statistical tests were two-sided, and $P$ values of 0.05 or less were considered to indicate statistical significance.

**TROCODILE Meta-analysis**

Data from all published and unpublished randomized trials in locally advanced (stage IIIA-B) NSCLC in which, after induction chemotherapy, a concurrent taxane-based chemo-radiotherapy strategy vs radiotherapy alone were compared were sought. After the same induction chemotherapy in both arms, the control and experimental arms had to differ only by presence or not of concomitant taxanes-containing chemotherapy (paclitaxel or docetaxel). Therefore, all randomized
trials with the following design were considered: induction chemotherapy (same drugs and schedule in the control and experimental arms) followed by radiotherapy (same fractionation and dosage in the control and experimental arms) vs induction chemotherapy followed by paclitaxel or docetaxel combined with radiotherapy. Studies testing the administration of taxane as single-agent or combined with other agents (e.g. weekly carboplatin plus paclitaxel) were both eligible.

Eligible trials were identified by regular computer-aided searches, through literature databases (MEDLINE, CANCERLIT), examining reference lists of published trials, review articles, searching ASCO, ESMO and WCLC meeting abstracts from 2009 to 2014, and consulting trials registers (US National Cancer Institute Physicians Data Query Clinical Protocol). For databases research the following strategies were used: “Chemotherapy [MeSH] AND Radiotherapy [MeSH] AND Carcinoma, Non-small-cell lung/drug therapy [MeSH] AND Clinical trial [pt]” and “Chemotherapy AND Radiotherapy AND Locally Advanced Non-small cell lung cancer”

Primary measure of outcome for the meta-analysis was the odds ratio (OR) of being alive 1 year after randomization for experimental arm (radiotherapy plus taxane) versus control arm (radiotherapy alone). We chose this measure at a fixed time point (1-year) because hazard ratio was not available for all the publications. The proportion of patients alive 1-year after randomization was extracted from the publication, when available, calculated from the Kaplan-Meier curves or obtained directly from the authors. After data were abstracted, meta-analysis was performed using RevMan 5.1 software, developed by the Cochrane Collaboration. A random-effects model was applied. Statistical heterogeneity between studies was examined using the $\chi^2$ test and the $I^2$ statistic.
Results

PITCAP Trial

Due to slow recruitment, accrual was terminated early, at the time of the second planned interim analysis, when 152 patients had been randomized from February 2000 to November 2004 at 26 Italian centres. Patient disposition is shown in Figure 1. One patient was excluded from the intention-to-treat because it was randomized twice by mistake. Patients characteristics of the 151 patients eligible for analysis are reported in Table 1. Patients characteristics were well balanced between the two arms. In summary, overall median age was 61 years; most patients were males (91%), 68% had stage IIIB, 60% had PS 0, 42% had squamous histology.

Overall, 44% of patients received cisplatin and 56% carboplatin in combination with paclitaxel in the induction chemotherapy program, with no difference between the two study arms. Induction chemotherapy was well tolerated, with 5.3% leukopenia and 20% neutropenia as the most frequent grade 3-4 side effects. One-hundred forty-four patients completed the 2 planned courses and a total of 294 courses were delivered, with only 1.7% dose-reduction and 4.2% treatment delays of cycle 2. Seventeen and 14 patients, respectively, did not proceed to consolidation radiotherapy, with or without weekly paclitaxel, due to either disease progression or clinical deterioration. Response rate to induction?

Among the 119 patients who started irradiation treatment, radiotherapy was completed as per protocol in in the majority (??%) of patients, with a median total RT dose of 60 Gy (delivered in 6 weeks in 53% of patients and 7 weeks in the remaining) in both arm. Nearly 80% of patients in experimental arm completed concurrent weekly paclitaxel as per protocol. Treatment toxicity was manageable in both arms (grade 3-4 esophagitis 4.3 vs 10%; p = 0.278); one toxic death was recorded in the concurrent chemoradiation arm. Altre tossicità? Site of progression according to treatment arm?

Overall response rate and median progression-free survival did not differ according to treatment (54% vs 52% and 6.7 vs 9.2 months, in the control and experimental arm, respectively) (Table 2).
With a median follow-up of 6.1 years, median survival was 13.2 vs 15.1 months with a 3-year survival rate of 19.5% vs 21.2% in the control and experimental arm, respectively (HR: 0.97; 95%CI 0.69-1.36; p = 0.845) (Figure 2). *Futility?*

**Meta-analysis**

Five further trials were identified [13-17]; one of these was not considered in the meta-analysis because the sequential chemo-radiotherapy arm was stopped early after 19 patients and its results were not reported in the final publication [17]. The remaining 4 trials and the present study were divided in two sub-groups according to the timing of randomization: after induction in three trials [13-15] and before induction in two trials [16 and PITCAP trial].

The meta-analysis showed no significant difference in the chance of being alive after 1 year between patients assigned to chemo-radiotherapy and patients assigned to radiotherapy arm. In detail, as shown in Figure 3, the proportion of patients alive after 1 year was 57.4% in both arms (OR: 1.00; 95%CI: 0.76-1.31; p = 1.00), without statistical heterogeneity among the 5 trials ($I^2 = 0$%; p = 0.85). As for subgroup analysis according to the timing of randomization, no significant difference was observed in the three trials performing randomization after induction (OR: 1.02; 95%CI 0.72-1.43; p = 0.93), nor in the two trials performing randomization before induction (OR: 0.97; 95%CI 0.62-1.52; p = 0.90).
Discussion

According to international guidelines [6, 18-20], concurrent platinum-based chemotherapy and thoracic irradiation is the recommended treatment for locally advanced inoperable NSCLC. This recommendation is based on the results of a series of randomized studies and meta-analyses demonstrating the superiority of concurrent chemo-radiation over radiotherapy alone [21, 22] and over sequential chemo-radiation [23-26] at the cost, however, of an increased toxicity [3]. On the contrary, induction chemotherapy preceding concurrent chemo-radiation [4] and consolidation chemotherapy after chemo-radiation [5], although still commonly used in clinical practice, have not been proved to add any efficacy in terms of long-term survival outcome to concurrent chemo-radiation alone.

However, despite the scientific evidence of its superior efficacy, in real world clinical practice concurrent chemo-radiotherapy is not applied to the majority of patients with locally advanced inoperable NSCLC. While in US, pattern of care surveys report the use of concurrent chemo-radiation in approximately ¾ of patients, similar studies in EU report lower use of concurrent chemoradiotherapy strategy. For example, De Ruyscher et al reported the results of a population-based study conducted in the Netherlands in which less than 50% of patients were treated with concurrent chemoradiation [9]. In Italy, the RIGHT3 survey showed little adherence to Italian Association of Medical Oncology Guidelines recommending concurrent chemo-radiation for stage III NSCLC [10].

The reasons of this discrepancy between scientific societies recommendation and real world clinical practice are manifold. First, eligibility for concurrent chemo-radiation is scanty due to inadequate location and volume of the tumor, advanced age, poor PS and presence of cardiovascular and respiratory co-morbidities. Second, physicians and patients are often worried about increased toxicity of concurrent chemo-radiation which may seem not justified in view of the little benefit in terms of increased cure rate as compared to other forms of less toxic integration of chemotherapy and radiation. Finally, in several areas of the world, busy radiotherapy departments with long
waiting lists and cumbersome treatment planning do not allow to start thoracic irradiation as early as chemotherapy. For all these considerations, when we planned the PITCAP trial, clinical practice for the treatment of locally advanced NSCLC in Italy was largely dominated by the use of sequential chemo-radiation approaches. In this contest, being aware of the data supporting the superiority of concurrent chemo-radiation, we aimed at assessing whether the addition concurrently to thoracic irradiation of a feasible and highly tolerable chemotherapy, such as weekly paclitaxel, could improve the outcome without worsening the feasibility of this chemo-radiation regimen.

Unfortunately, the accrual in the PITCAP trial was much lower than expected and the study had to be terminated earlier when half of the expected sample size was enrolled. Slow accrual is, unfortunately, a common theme in clinical trials of combined treatment of locally advanced NSCLC due to the complexity of the multidisciplinary approach, to the strict eligibility criteria and to stage migration with the increased use of PET scanning and brain CT/MRI in clinical staging.

Despite the limitation of a reduced sample size and of early accrual interruption, the results of our study point to the conclusion that weekly paclitaxel given concurrently to thoracic irradiation after platinum-paclitaxel induction chemotherapy, although feasible and very well tolerated, does not have a clinically meaningful effect on long-term survival outcome.

In the literature we could identify other 4 studies with similar design [13-16], 3 of which came to similar conclusions [14-16] (Table 3). Belani et al reported the results of US LAMP 3-arm trial including 276 stage III NSCLC patients testing two carboplatin-paclitaxel induction courses followed by standard thoracic irradiation with or without concurrent weekly carboplatin-paclitaxel, along with a third regimen consisting of the same concurrent chemo-radiotherapy program followed by 2 carboplatin-paclitaxel courses [16]. Median survival and 3-year survival rates were 13.0, 12.7, and 16.3 months and 17, 15 and 17%, respectively. Although the authors concluded that concurrent chemo-radiotherapy followed by consolidation seemed to produce best outcomes, the study was formally non comparative, and no solid conclusion could be derived about the efficacy of the addition of chemotherapy to thoracic irradiation following induction chemotherapy. Scagliotti et al
conducted an European 2-arm trial in 108 stage III NSCLC patients comparing cisplatin-docetaxel induction chemotherapy followed by standard thoracic irradiation alone or combined with concurrent weekly docetaxel [14]. Survival outcomes were superimposable in the two treatment regimens. Huber et al enrolled 303 inoperable stage III NSCLC patients in a German randomized trial with identical design to the PITCAP Italian trial [13]. In this study, the addition of weekly paclitaxel to thoracic radiotherapy after induction carboplatin-paclitaxel led to a non-statistically significant numerical increase in median survival (14.1 vs 18.7 months). Brunsvig et al conducted a phase III trial where 249 NSCLC stage IIIA-B patients after 2 cycles of carboplatin-docetaxel were randomized to receive weekly docetaxel combined with radiotherapy or radiotherapy alone, obtaining similar survival outcome in two arms [15].

In all these studies results, both in terms of overall outcome and of relative benefit of concurrent chemotherapy, were remarkably similar with median survival of about 13-15 months regardless of treatment arm and of the type of concurrent chemotherapy regimen used. The TROCODILE meta-analysis included all these 5 studies. Although some heterogeneity was evident due to the different timing of randomization (up-front vs after induction), use of paclitaxel or docetaxel, use of carboplatin with paclitaxel concurrently with radiotherapy in US trial, all the available evidence suggests no significant benefit with the addition of taxane-based chemotherapy to thoracic irradiation. This result may seem in contrast with the data supporting concurrent chemo-radiation. However, all the evidence favoring the superiority of concurrent over sequential chemoradiation and radiation alone has been obtained with trials using platinum-based chemotherapy regimens starting concurrently with radiotherapy, without previous induction chemotherapy [21–26]. Other two randomized trials assessing the role of single agent carboplatin given concurrently to thoracic irradiation after induction chemotherapy also led to negative results [27, 28]. It might therefore be reasoned that induction chemotherapy could hinder the benefit of the subsequent chemotherapy given concurrently with radiotherapy. A plausible biological explanation of this negative effect of induction chemotherapy could be the early induction of chemotherapy resistance and/or the
recruitment of proliferating neoplastic cells as it has been shown in experimental models [29].

Of course, differently from a meta-analysis based on individual patient data, our literature-based meta-analysis has some intrinsic limitations, the most relevant being the different timing of randomization among trials and the unfeasibility of exploratory subgroup analysis to test the presence of interaction among main patients’ characteristics and treatment efficacy.

In conclusion, the results of PITCAP trial together with those of TROCODILE meta-analysis, do not support a clinically meaningful benefit with the addition of taxane-based chemotherapy given concurrently to thoracic irradiation after platinum-based chemotherapy induction in locally advanced inoperable NSCLC. In patients where upfront chemo-radiation, which remains the optimal treatment option for ideal candidates, is not feasible and induction chemotherapy followed by thoracic irradiation is planned, radiotherapy can be delivered alone without the addition of further chemotherapy.
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Figure Legend

Figure 1: Consort Diagram.

Figure 2: Kaplan Meyer Survival Curves (panel A: PFS; panel B: OS).

Figure 3: Forest Plot Meta-Analysis.
Appendix: Participating Institutions

Parma: Franciosi 4
Perugia: Crinò 4
Regina Elena: Francesco Cognetti, Arcangeli 4
Cuneo: Marco Merlano, Elvio Russi 3
Torino: Fornari 3
Lugo Ravenna: Cruciani 3
Pisa: Conte, Cionini, Silvano 3
Bergamo: La Bianca 3
Brescia Frata 3
Terni: Di Costanzo 2
Asti: Testore 2
Monza: Ardizzoia 1
Ivrea: bretti 1
Ravenna: marangolo 1
Roma s.camillo: 1